Cerebral white matter changes

Differentiating vascular and degenerative cognitive impairment

by

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In memory of

Petter André

"Clap your hands and move your feet

to the rhythm of the beat"

Dr. Johann Wasmaier

CONTENTS

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LIST OF PUBLICATIONS

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1. INTRODUCTION

"Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. This syndrome occurs in Alzheimer's disease, in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain."

(World Health Organization ICD-10, 2007)

Different types of dementia are difficult to identify *in vivo*, especially at early stages and partly due to the frequent co-existence of various etiologies. Recent techniques, including examination of biomarkers in cerebrospinal fluid (CSF) and advanced brain imaging techniques facilitate a more precise diagnosis of a given type of dementia. As previous diagnostic criteria for the Alzheimer type of dementia (AD) only captured the disease after dementia occured, new criteria involving recent biomarkers aim to arrive at a diagnosis at early stages, even prior to the onset of overt dementia. Along with episodic memory impairment, neuroimaging and CSF analysis have been proposed as reliable and important tools to make an accurate AD diagnosis possible, including forms of AD with co-existing cerebrovascular disease.

The objective of this thesis aims to exploit the posssibilities of CSF analysis and neuroimaging in order to better understand the relationship between cerebrovascular and degenerative changes and cognition. To do so, measures of cerebral white matter changes from magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) were studied in cognitively impaired patients and compared to levels of CSF biomarkers and cognition. In degenerative and vascular cognitive impairment, risk factors and pathological disease processes have been well mapped. However, it remains unclear which exact mechanisms trigger these processes and in which way white matter changes and cortical events are connected. Improved early diagnostic specificity and better knowledge of interaction between vascular and degenerative changes may give rise to specific approaches to prevention and therapy, based upon individual risk-profiles.

1.1 Leukoaraiosis

1.1.1 Background

The increased availability of computer tomography (CT) and MRI in clinical practice beginning in the 1970´s and 1980´s revealed cerebral white matter changes in both normal elderly and cognitively impaired individuals (Verny et al., 1991; Meyer et al., 1992). The observed white matter changes (presenting as diffuse low density areas on CT scans and as areas of hyperintensity on T2- and FLAIR-weighted MRI scans) were often considered to be an expression of leukoencephalopathy associated with Binswanger`s disease (Hachinski et al., 1987; Inzitari and Mascalchi, 1990; O'Sullivan, 2008). In the need for a more neutral term, Hachinski and colleagues suggested the term Leuko-araiosis (*leuko* = white, *araiosis* = rarefaction) on the basis of Greek etymology (Hachinski et al., 1987). It was suggested to avoid the term "Binswanger" when describing these white matter rarefactions (Pantoni and Garcia, 1995). White matter changes (WMC), white matter hyperintensities (WMH), and white matter lesions (WML) are now commonly used terms.

1.1.2 Etiology

Periventricular and deep white matter areas are supplied by long penetrating arterioles originating from pial arteries (De Reuck, 1971; Salamon et al., 1966). WML in the elderly are associated with microvascular disease leading to ischemia and hypoperfusion (Fernando et al., 2006; Roman et al., 2002; Ward and Brown, 2002). Age, hypertension, and hyperhomocysteinemia are known risk factors for both arteriolosclerosis and WML (Bertsch et al., 2001; Breteler et al., 1994; Vermeer et al., 2002) and post mortem pathological associations between WML and arteriolosclerosis have been described (Awad et al., 1986; van Swieten et al., 1991). There is a strong correlation between age-related WML and vascular risk factors (de Leeuw et al., 2002). In most patients, cognitive impairment associated with WML is regarded primarily as a vascular cognitive disorder (Roman, 2002; Roman et al., 2004).

WML may affect both periventricular (PV) and subcortical (SC) white matter (de Groot et al., 2000a; Fazekas et al., 1993), with PV regions lying in the distal part of the perfused region. Ischemic WML may therefore develop as a result of ischemia caused by arteriolosclerosis, which starts distally in deep penetrating end arterioles as

suggested by post-mortem studies (De Reuck, 1971; Englund, 2002; Pantoni, 2002; Roman et al., 2002; van Swieten et al., 1991; Simpson et al., 2007).

SC and PV WML subtypes show many similarities with regard to pathogenesis, but substantial differences in tissue response and vascular risk factors between WML in the two regions have been described (Simpson et al., 2007; Lazarus et al., 2005). However, the strong correlation between PV and SC WML suggests etiopathological similarities, implying that these lesions may be manifestations of a single underlying disease process. In this view, PV and SC WML may represent a continuum of neurovascular pathology (DeCarli et al., 2005).

Alternative mechanisms for WML development cannot be excluded. WML have been related to gliosis, demyelination and axonal loss (Awad et al., 1986; Fazekas et al., 1993; van Swieten et al., 1991; Ward and Brown 2002, see below), and genetic factors may also have a strong influence on the development of leukoaraiosis. A study quantifying leukoaraiosis in monozygotic and dizygotic twins suggested that as much as 71% of the cerebral white matter lesion volume could be explained by heritability (Carmelli et al., 1998). Genes affecting blood pressure or other (metabolic) pathways have been proposed as possible contributors (Turner and Fornage, 2002).

In addition to reduced cognitive function, white matter lesions have been associated with depression, gait disturbances and disability in the elderly (de Groot et al., 2000b; Pantoni et al., 2006; Teodorczuk et al., 2007; Baezner et al., 2008)

1.1.3 Quantification of white matter lesions

Several semi-quantitative visual rating scales are available for the grading of white matter lesion severity. Some scales differentiate only into normal, moderate, and severe WML load (van Swieten et al., 1991), while others divide WML into periventricular and subcortical, as well as into different anatomical regions (de Groot et al., 2000a; Fazekas et al., 1987; Scheltens et al., 1993;Wahlund et al., 2001). Other methods include semi-automated volumetric approaches as well as computer-assisted volumetric measurements and segmentation methods (DeCarli et al., 1995; Gurol et al., 2006). These various approaches have in common that they measure white matter damage as seen on CT or conventional MRI scans. As WML may be associated with white matter affection beyond lesions visible on conventional MRI (Taylor et al., 2007, O´Sullivan et al., 2001), these commonly used methods may not

adequately reveal the underlying but visually hidden white matter pathology.

1.2 Cognitive Impairment

1.2.1 Mild Cognitive Impairment (MCI)

Individuals with cognitive impairment but preserved performance of activities of daily living who do not meet criteria for overt dementia are referred to as patients with mild cognitive impairment (MCI) (Petersen et al., 2001; Petersen et al., 1999). According to the original criteria (Peterson et al., 1999), besides subjective memory impairment, preserved general intellectual function, intact ADL, and absence of overt dementia, objective memory impairment must be present to meet the diagnostic criteria for MCI (amnestic MCI). In the recently revised MCI criteria (Winblad, et al., 2004) also patients without memory impairment, but with deficits in other cognitive domains may be classified as MCI (non-amnestic MCI). In particular patients with amnestic MCI are at risk of developing AD, and 40-60% will convert to AD within 5 years (Petersen et al., 2004). MCI etiology clearly is heterogeneous. In order to understand pathogenetic mechanisms and in order to enable development of disease modifying drugs it is important to recognize the underlying pathology at an early stage (DeKosky and Marek, 2003).

Structural and functional imaging studies have revealed alterations of the posterior cortex including posterior cingulate gyrus and the medial temporal lobe (MTL) in patients with MCI and AD. Compared to normal controls, a reduced volume of the entorhinal cortex and hippocampus has been observed in MCI patients (Convit et al., 1997; Du et al., 2001). The determination of hippocampal volume may thus contribute to the prediction of AD development in patients with MCI (Jack et al., 1999). Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) studies have revealed reduction of glucose metabolism in the MTL and posterior cingulate cortex of MCI patients, especially in ApoE-ε4 carriers (Mosconi, 2005).
Due to the high rate of patients with MCI who develop AD, MCI is commonly considered as clinical pre-AD. Imaging techniques and cerebrospinal fluid (CSF) biomarkers (see below) may be helpful to identify incipient AD in MCI patients.

Subjective cognitive impairment (SCI) has recently been suggested as a pre-MCI stage in a possible SCI-MCI-AD disease continuum (Reisberg and Gauthier, 2008), making this population interesting for longitudinal studies as well.

1.2.2 The Neurobehavioral Cognitive Status Examination (Cognistat)

The Neurobehavioral Cognitive Status Examination (Cognistat) (Kiernan et al., 1987; Schwamm et al., 1987) is a test of cognitive function. It usually takes less than 45 minutes to complete, depending on the cognitive status of the patient, which makes it suitable for use in the testing of large samples. However, it is important that trained staff performs the test. Cognistat includes subtests for orientation, attention, comprehension, repetition, naming, visuoconstruction, memory, calculation, similarities (verbal abstraction and concept formation), and judgment. The memory scale tests delayed verbal memory and includes cued recall. In the beginning of the test, the examiner asks general questions about the patients name, age, etc, before the examiner asks questions related to orientation (place and time). Next, the examiner tests memory and attention. Verbal memory is tested and the patient is asked to repeat a series of digits. The patient will be asked to recall the items he/she was asked to remember earlier. Spontaneous speech is tested by asking the patient to describe a detailed drawing. Language ability is further tested by observing the response to simple commands (comprehension) and by asking the patient to repeat phrases and sentences (repetition). In the last subtest of the language section, naming, the patient is asked to name parts of separate object when pointed to. Constructional ability is tested by having to draw an item, which was presented, on a stimulus sheet for ten seconds. Constructional ability is tested as the patient must fit plastic tiles into designs shown on a card. Calculation is tested by simple verbal mathematics. Reasoning consists of two subtests (similarities and judgment). Similarity is tested as the patient must explain in which way two concepts are similar. In the subtest for judgment the patient must show his/her ability to solve basic problem scenarios by answering questions demonstrating practical judgment.

1.3 Alzheimer's disease

1.3.1 Background

Accounting for approximately 60% of all dementia cases, Alzheimer's disease (AD) is the most common cause of dementia in the industrialized nations. In 2006, the worldwide prevalence was estimated at 26 millon , a number expected to quadruple in the next 40 years. This means that 1 in 85 persons will be affected by 2050 (Brookmeyer et al., 2007). In the western world, the AD prevalence in people older than 85 years of age is around 30%. Besides cancer, stroke, and cardiovascular

disease, AD has become one of the major causes of morbidity in the developed nations (Blennow et al., 2006; Tedeschi et al., 2008). This renders AD into a major public health problem. If early diagnosis and treatment could help delay disease onset and progression by as little as one year, the global AD burden would be significantly reduced (Brookmeyer et al., 2007).

AD is neuropathologically characterized by loss of synapses, neuron degeneration, extracellular senile plaques, and intracellular neurofibrillary tangles. The amyloid cascade hypothesis is an important hypothesis for the cause of AD. Imbalance in Aβ production and clearance lead to Aβ aggregation and formation of plaques. Recent research has highlighted the neurotoxicity of diffusible Aβ oligomers (Blennow et al., 2006; Walsh and Selkoe, 2004). The formation of neurofibrillary tangles, another major component of AD pathogenesis, is believed to cause axonal dysfunction thereby compromising neuronal and synaptic function (Iqbal et al., 2005). Neurofibrillary tangles consist of abnormally hyperphosphorylated tau protein (Grundke-Iqbal et al., 1984). Tau is a microtubule-associated protein mainly located in neuronal axons. It is important for the stabilization of microtubuli and axonal maintenance (Drubin et al., 1988). However, it is yet not clear whether tau pathology and tangle formation are a cause or a consequence of the AD disease process.

According to the amyloid hypothesis of AD, β-amyloid or precursors cause both nerve cell loss and memory failure. Genes causing familial early onset AD show non-allelic heterogeneity and are all related to metabolism of amyloid. The only established genetic risk factors for late onset AD, Apolipoprotein E, may be related to both amyloid metabolism and to the development of cerebrovascular pathology (see later in text).

There are three high penetrance genes which have been related to early onset familial AD. β-amyloid precursor protein (APP), is located on chromosome 21 and is triplicated in Down syndrome, possibly accounting for the early development of Alzheimer´s disease in trisomy 21 individuals. Families with autosomal dominant early onset Alzheimer´s disease harbor point mutations in APP, leading to amino acid changes at proteolytic sites for α, β, and γ-secretases that normally are involved in processing the APP protein. Two other genes related to early onset familial AD are presenilin 1 and 2, located on chromosomes 14 and 1 respectively. Mutations in these genes are the most common causes of familial AD and they have been shown to

increase production or alter the ratio of amyloid peptides (Aβ1-40 and Aβ1-42) (Selkoe, 2002).

Histopathological confirmation still is the gold standard for a definite AD diagnosis. The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) have defined criteria for probable AD. The diagnosis of probable AD is based on clinical and neuropsychological examination, the presence of cognitive impairment confirmed by neuropsychological testing along with exclusion of other causes of dementia. The use of CT and MRI scans in the context of these criteria is essential to identify alternative causes of cognitive impairment (brain tumors, normal pressure hydrocephalus, subdural haematomas, etc) as well as concomitant cerebrovascular disease (Blennow et al., 2006).

New scientific knowledge about early AD, proteomic findings, and the availability of functional and structural imaging has led to a revision of the NINCDS-ADRDA criteria for research purposes (Dubois et el., 2007). As new AD biomarkers have become available, the new criteria propose the use of MRI, positron emission tomography (PET), and CSF analysis not only for exclusion of alternative causes of dementia, but as specific supportive criteria in addition to episodic memory impairment.

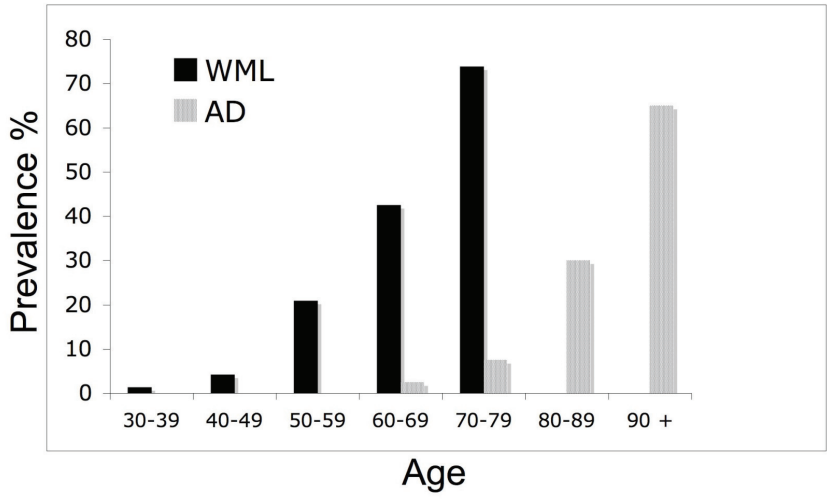
1.3.2 Alzheimer's disease and white matter changes

Small vessel disease and AD often coexist and patients with cerebrovascular disease have increased risk for AD (de la Torre, 2002; Snowdon et al., 1997). Clinical distinction between the two entities may be difficult, as both AD and microvascular disease lack focal signs initially and progress insidiously. In addition, ischemic brain disease and WML may also be etiologically linked to AD (Snowdon et al., 1997; Vermeer et al., 2003).

Established risk factors for vascular disease like hypercholesterolemia, hypertension, and hyperhomocysteinemia may increase the risk for sporadic AD (Gorelick, 2004; Napoli and Palinski, 2005; Casserly and Topol, 2004), and a reduced risk for AD after treatment of hypertension and hypercholesterolemia has been described (Casserly and Topol, 2004; Forette et al., 2002; Fassbender et al., 2001; Lim et al., 2005).

Figure 1 shows the prevalence of WML and AD according to age group. WML occurs earlier than AD, supporting the hypothesis that cerebrovascular events increase the risk of AD.

Figure 1: WML and AD prevalence adapted from Masani et al., 2003 and Hy et al., 2000.



WML prevalence precedes AD prevalence by 20 to 30 years.

WML have been associated with hippocampal atrophy in AD (de Leeuw et al., 2004), and a recent study of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) suggests that subcortical vascular lesions are associated with low CSF Aβ42 (Formichi et al., 2008). Experimental studies have suggested mechanisms that could account for this effect. Ischemic changes in the surroundings of neuronal tracts may lead to glial activation, formation of amyloid precursor protein (APP), and release of diffusible agents that may induce apoptosis (Sachdev et al., 2004; Wallin et al., 2000; Melton et al., 2003; Badan et al., 2003; Jin et al., 2001; Nihashi et al., 2001). After experimental white matter damage, studies suggest that amyloid could be deposited in the disconnected

cortical regions, or APP could be transported to cortical regions from the site of damage along neuronal tracts (Yam et al., 1998; Murakami et al., 1998).

It has also been proposed that Wallerian degeneration may contribute to white matter changes (Englund, 1998; Leys et al., 1991). Supporting this notion, altered white matter myelination and a relationship between white matter gliosis and parenchymal Aβ load have been described in AD patients (Chalmers et al., 2005; Roher et al., 2002). WML in patients with AD may therefore partly arise secondary to cortical pathology. However, white matter degeneration has also been found in patients with early AD without signs of cortical thinning (de la Monte, 1989), suggesting that white matter is affected before cortical degeneration occurs. Diffusion alterations in parahippocampal white matter of AD patients have been observed as well, and after correcting for hippocampal volume (Salat et al., 2008). These findings suggest that white matter alterations may represent an additional mechanism, besides cortical degeneration, in the AD disease process.

1.4 White matter changes and cognition

WML may affect subcortical-cortical networks, as well as cortical association and projection fibers, leading to cortical disconnection and causing cognitive affection (Catani and Ffytche, 2005; Nordahl et al., 2006; O´Sullivan et al. 2004).

WML are associated with cognitive loss and dementia (Artero et al., 2004; Prins et al., 2002, Prins et al., 2004), but the associations reported between ischemic WML and cognition are variable (Au et al., 2006; Breteler et al., 1994; Burns et al., 2005; de Groot et al., 2000a; Hunt et al., 1989; Longstreth et al., 1996; Reed et al., 2007; Sabri et al., 1999). Executive functions and information processing speed are most consistently found to be affected, whereas affection of memory is a less consistent finding (Catani et al., 2005; Jokinen et al., 2006; Prins et al., 2005; Salamon et al., 1966; Soderlund et al., 2006). The variability of the findings may be due to differences in methodology and different patient groups with various types of co-existing brain disease.

Both PV and SC WML have been associated with impaired cognition (de Groot et al., 2000a; Baum et al., 1996; Burns et al., 2005; Delano-Wood et al., 2008; Gold et al., 2007; Soderlund et al., 2006). However, the findings are inconsistent and it is not clear to what degree the effects of PV and SC WML on cognitive function differ. Due to separate anatomical locations, PV and SC WML affect different fiber

tracts. PV lesions most likely affect projection and longer distance association fibers, whereas SC lesions affect short distance association fibers and cortical-subcortical networks (Brodal, 1998). These differences may lead to different modalities of impairment of cognitive function.

As most cognitive capabilities are sensitive to the effects of AD, particularly delayed recall, the effects of WML alone are difficult to detect. Therefore, a subpopulation of patients without manifest or incipient AD is required to study the specific cognitive effects of WML. The use of CSF biomarkers is one possible way to stratify patients with cognitive impairment into groups more or less likely to suffer from incipient AD.

As a part of the Papez-circuit (Papez, 1937), the posterior cingulum fibers play an important role in memory function as they connect the posterior cingulate gyrus with the medial temporal lobe (Buckner et al., 2005; Catani et al., 2002; Crosby, 1962). A number of recent studies have focused on cingulum fibers using diffusion tensor imaging (DTI). These studies have shown that white matter diffusion parameters correlate with working memory in healthy middle-aged and elderly adults (see below).

1.5 Cerebrospinal fluid biomarkers

The use of CSF biomarkers may contribute to early detection of AD (de Leon et al., 2007). Such markers have been suggested as adjunct markers for the diagnosis of "probable AD" in patients with episodic memory deficits (Dubois et al., 2007).

CSF biomarkers (tau and beta-amyloid proteins) for AD have a diagnostic specificity and sensitivity of around 85% (Blennow and Hampel, 2003; Wiltfang et al., 2005). These markers have been shown to predict the development of clinical dementia and AD in patients with MCI (Diniz et al., 2007; Hampel et al., 2004; Hansson et al., 2006). In addition, these CSF biomarkers have been shown to distinguish AD in patients with vascular dementia, irrespective of co-existing subcortical cerebrovascular disease (Stefani et al., 2005). CSF biomarkers possess high sensitivity to differentiate early AD from normal aging, depression, Parkinson's disease, and alcohol dementia, but lower specificity with respect to other types of dementias, such as fronto-temporal and Lewy body dementia (Andreasen and Blennow, 2005).

Low levels of CSF Aβ42 have consistently been observed in patients with AD (Andreasen et al, 1999; Blennow and Hampel, 2003). An inverse correlation between CSF Aβ42 levels and brain amyloid deposition has been established in pathological studies (Strozyk et al., 2003), including in-vivo amyloid imaging studies (Fagan et al., 2006; Forsberg et al., 2007). Experimental evidence further suggests that the reduction of Aβ42 seen in AD may be partly due to Aβ42 deposition in amyloid plaques (Kawarabayashi et al, 2001). However, one should not loose sight of the fact that Aβ42 serves as a surrogate marker, and reduced levels may also be seen in other neurodegenerative diseases (Sjogren et al., 2002; Otto et al., 2000; Noguchi et al., 2005; Mollenhauer et al., 2005).

Elevated CSF levels of total Tau protein (T-tau) and phospho-Tau (P-tau) have been observed in different neurodegenerative diseases and are probable markers for axonal damage and tangle formation (Blennow and Hampel, 2003; Sunderland et al., 2003; Sussmuth et al., 2001; Teunissen et al., 2005). High levels of CSF T-tau may indicate the extent of neuronal damage. In the rapid progressive neurodegenerative disorder Creutzfeldt-Jakob disease (CJD), very high levels of CSF T-tau have been observed (Otto et al., 1997; Skinningsrud et al., 2008). Likewise, in acute ischemic stroke a positive correlation between increased CSF T-tau and the size of the infarction have been reported (Hesse et al., 2000). The P-tau isoform does not seem to be elevated in acute ischemic stroke or CJD. Since this particular isoform represents the phosphorylation state of tau protein in the brain it may be a better marker for AD (Blennow and Hampel, 2003).

In combination with careful clinical examination, medical history, and brain imaging, CSF biomarkers may in fact increase the diagnostic accuracy in early AD.

1.6 Apolipoprotein E

Apolipoprotein E-ε4 (ApoE-ε4) carrier status is the only well established genetic risk factor for late onset AD (Corder et al., 1993). APOE is a protein with many different functions related to lipid metabolism and lipid transport between cells (Herz and Beffert, 2000). The gene is located on chromosome 19, and three common isoforms are known in humans (ApoE-ε2, ApoE-ε3, and ApoE-ε4). The isoform ApoE-ε4 has been related to increased risk of developing AD (Farrer et al., 1997). For patients who

carry two ApoE-ε4 alleles, the chance of developing AD by the age of 85 is in the order of 50% to 90% (Corder et al., 1993).

It is yet not clear through which mechanisms ApoE-ε4 increases the risk for AD. However, considerable evidence indicates that ApoE-ε4 may interact with APP processing and induce aggregation and binding, as well as cause reduced clearance of β-amyloid (Wisniewski et al., 1993; Strittmatter et al., 1993; Holtzmann et al., 2000; Bales et al., 1997). ApoE-ε4 has also been related to cardiovascular and cerebrovascular disease (Eichner et al., 2002; McCarron et al., 1999). In particular small vessel disease (arteriolosclerosis) and micro infarcts have been associated with ApoE-ε4 in brains of AD patients (Yip et al., 2005), and ApoE-ε4 positive AD patients have higher WML load than ApoE-ε4 non-carriers (Bronge et al., 1999). The latter suggests that ApoE-ε4 may play a role in the cerebrovascular pathology frequently observed in AD patients. However, the role of the different ApoE genotypes in the development of cerebrovascular disease and WML needs to be further clarified (for review see Turner and Fornage, 2002).

1.7 Diffusion Tensor Imaging

1.7.1 General background

Diffusion tensor imaging (DTI) can be used to quantify white matter integrity (Le Bihan et al., 2001). DTI may reveal white matter changes and degradation of white matter fiber bundles not detectable with conventional MRI (Deo et al., 2006; Taylor et al., 2007). DTI techniques are mostly based on diffusion of water molecules. Diffusion of molecules is restricted by cell membranes and fiber structures. In cerebral white matter, axonal membranes and myelin represent such barriers and diffusion parallel to fiber bundles is greater than perpendicular diffusion. The principle of restricted molecular mobility in some directions is called “diffusion anisotropy”. Fractional anisotropy (FA) can be calculated from the diffusion tensor eigenvalues and is a measure of directional diffusivity (Basser et al., 1994; Le Bihan et al., 2001). FA varies between 0 (isotropic diffusion / equal diffusion in all directions) and 1 (entirely anisotropic / undirectional diffusion). The FA parameter is expected to be reduced when axonal damage or dysmyelination occur. Mean diffusivity (MD) is a measure of diffusion averaged in all directions and indicates the magnitude of diffusion. MD will typically increase when axonal membranes or

myelin are damaged (Le Bihan et al., 2001; O´Sullivan et al., 2001; Ulug et al., 1999).

The diffusion eigenvalues may be separated into components, which describe diffusivity parallel (λ1) or perpendicular (λ2 and λ3) to the axonal tracts (Basser et al., 1994; Xue et al., 1999). Axial diffusivity (DA, parallel to axon tracts) and radial diffusivity (DR, perpendicular to axon tracts) may be helpful to better describe the underlying pathology of white matter alterations reflected by FA (Wang et al., 2008). After experimental ischemia, reduced DA is followed by increased DR mirroring the sequence of Wallerian degradation of axons and myelin components in the CNS (George and Griffin 1994a; George and Griffin 1994b; Sun et al., 2008). It has been suggested that decreased DA may reflect axonal loss and that increased DR may be associated with dysmyelination (Pierpaoli et al., 2001; Song et al., 2003; Song et al., 2002). Parts of the DA and FA changes observed in the acute phase after axonal damage may be transient, and DR changes observed in the chronic stage after axonal damage may represent myelin degradation (Concha et al., 2006). Experimental evidence from contusion injuries also suggests that changes in DR are sensitive to secondary changes beyond the site of the primary histologically defined lesion (Budde et al., 2007).

Studies have reported an association between age-related cognitive decline and reduced FA (Charlton et al., 2006). In addition, reduced (FA) in posterior cingulum fibers has been observed in MCI patients compared to normal controls (Fellgiebel et al., 2005; Zhang et al., 2007). Few studies have examined directional diffusivity (DR and DA) in MCI and AD patients, and so far the findings have been inconclusive. One study reported reduced DA, consistent with axonal degeneration, in the temporal lobe of AD and MCI patients (Huang et al., 2007), whereas another study focused on frontal regions and found signs of altered myelination (increased DR) in frontal white matter of early AD patients (Choi et al., 2005).

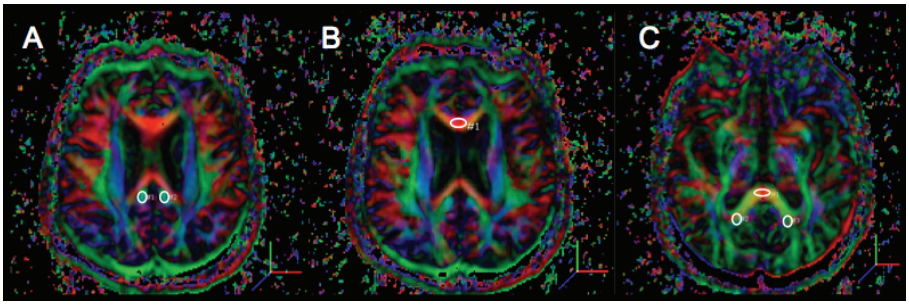
1.7.2 Regions of interest (ROI) analysis

The manual placement of regions of interest (ROI) in known white matter fiber tracks is a common method to measure diffusion parameters. First, MD, FA, individual eigenvalue images, and color-coded eigenvector (cDTI) maps are generated. In the cDTI maps the pixel color and intensity reflect the principal diffusion direction and FA magnitude, respectively. The nordicICE Basis and Diffusion Modules (NordicImagingLab AS, Bergen, Norway) is a preferred software that may be used

for this purpose, but other programs for DTI processing are available (Zhang et al., 2007).

When placing the ROI it is important to ensure that partial CSF or grey matter volume is avoided. This can be done by co-alignment of the DTI data (b=0 scans) with the MP-RAGE images (e.g. by using Statistical Parametric Mapping (SPM5), Wellcome Trust Centre for Neuroimaging, London, UK). White matter segmentations may then be created from the co-registered MP-RAGE sequence using the segmentation module provided by SPM5. The white matter masks as well as the cDTI maps may be used for orientation to avoid possible artifacts due to partial CSF or grey matter volume. ROI are usually placed in the part of the fiber tract with the highest signal intensity. To ensure the proper anatomical placement of the ROI between subjects, it is helpful to use the cDTI map in addition to comparing images.

Figure 2: Illustration of region of interest (ROI) placements



The figure illustrates the placement of regions of interest (ROI) in the color-coded (cDTI) map. ROI are shown in Cingulum fibers (A), genu corpus callosum (B), splenium corpus callosum and forceps major (C).

2. AIMS OF THE PRESENT STUDY

The main goal of the present work was to examine the relationships between white matter changes, risk factors for cerebrovascular disease and CSF biomarkers for Alzheimer disease (AD), but we also asked whether and how white matter changes relate to cognition in patients with cognitive impairment. Within the framework of this thesis, we posed and attempted to answer the following specific questions:

Is there a link between white matter lesions and amyloid pathology?
The relationship between cerebrovascular disease and cerebral degenerative disease has been widely studied, with experimental data showing that there might be a link between ischemia and amyloid deposition. We therefore aimed to test this hypothesis in patients with cognitive impairment by investigating a possible relationship between white matter lesion (WML) load (as a measure of cerebrovascular disease) and the CSF biomarker Aβ42 (a surrogate marker for amyloid deposition in the brain) (Paper I).

Do ApoE genotype and white matter lesions interact in the development of amyloid pathology?
Both cerebrovascular disease and ApoE-ε4 are known risk factors for AD. Paper I showed that both WML and the ApoE-ε4 genotype might increase the risk of having low CSF Aβ42. These findings led to the hypothesis that these two important risk factors for AD might interact (paper IV) in the development of amyloid pathology as measured by CSF Aβ42. Paper IV aimed to test this hypothesis by analyzing the risk of having low CSF Aβ42 in ApoE-ε4 carriers versus non-carriers in patient cohorts with either low or high WML loads.

Are white matter lesions related to cognitive loss, and does the location of white matter lesions matter?
WML appear in all areas of the cerebral white matter and consistently affect fiber tracks connecting areas of the brain, which are important for cognitive function. WML has therefore been related to axonal damage and gliosis in imaging and histo-pathological studies. If WML lead to damage of fiber tracks it is conceivable that

WML will affect cognitive function. As most cognitive capabilities are sensitive to the effects of AD, particularly delayed recall, a sub-population of patients without manifest or incipient AD is needed to study the specific cognitive effects of WML. For this purpose, we decided to compare effects of WML on cognitive loss in patients with normal and pathological CSF Aβ42 values (Paper II).
The relationship between subtypes of WML – periventricular (PV) and subcortical (SC) – is not yet clear. There is experimental evidence of closely related underlying pathomechanisms, but some studies argue that these WML subtypes represent entirely different disease processes. The location of these WML also suggests that they affect different fiber tracks, and therefore will affect cognition in different ways. For this reason, we aimed to investigate the co-existence of WML subtypes and their relation to cognitive impairment (paper III).

Are diffusion tensor parameters related to Tau pathology and could these changes be part of the development of mild cognitive impairment?
Reduced white matter integrity investigated with diffusion tensor imaging (DTI) has been observed in patients with mild cognitive impairment (MCI) compared to normal controls, particularly in areas related to the memory network. DTI parameters reflect reduced white matter integrity and axonal damage. Also, Tau pathology may reflect axonal dysfunction. As Tau protein in CSF has been shown to be elevated in patients at risk of developing AD, we hypothesized that white matter diffusivity changes would be more apparent in patients with elevated CSF T-tau levels than in patients with normal T-tau levels (paper V).

3. ABSTRACTS / SUMMARY OF RESULTS

Paper I

Associations between white matter lesions, cerebrovascular risk factors, and low CSF Aß42

Objective: To analyze a putative relationship between white matter lesions (WML), risk factors for WML, and Alzheimer disease (AD) as measured with the surrogate marker CSF Aβ42.

Methods: We analyzed effects of acquired risk factors for cerebrovascular disease and WML on AD as measured with an intermediate marker, CSF Aβ42. A total of 127 consecutive patients with subjective memory impairment (mean age 66 years; 57 women) investigated at a university-based memory clinic had brain MRI scans. WML were rated on a 12-point scale with a semi-quantitative procedure. We used path analysis with established and possible risk factors for WML and for reduced CSF Aβ42 (age, hypertension, hyperhomocysteinemia, hypercholesterolemia, APOE-ε4) as variables.

Results: The WML score was 1.5 points higher ($p<0.05$) in hypertensive than in non-hypertensive patients, and 1.9 points higher ($p<0.05$) in patients with hyperhomocysteinemia than in those with normal homocysteine levels. Hypercholesterolemia increased the probability of low CSF Aβ42 levels by 0.2 ($p<0.05$). For each point increase in WML score the probability of low CSF Aβ42 levels increased by 0.03 ($p<0.05$). APOE-ε4 was associated with reduced CSF Aβ42 ($p<0.01$).

Conclusions: Hypercholesterolemia, APOE-ε4, and white matter lesions may contribute to low CSF Aβ42 by independent mechanisms.

If WML load increases the risk of low CSF Aβ42 levels and reduced levels of CSF Aβ42 levels are associated with amyloid deposition, this indirectly implies a relationship between ischemic changes in white matter and cortical pathology as seen in Alzheimer's disease.

Paper II

White matter lesion severity is associated with reduced cognitive performances in patients with normal CSF Aβ42 levels

Objective – To identify possible associations between white matter lesions (WML) and cognition in patients with memory complaints, stratified in groups with normal and low CSF Aβ42 values.

Material and Methods – 215 consecutive patients with subjective memory complaints were retrospectively included. Patients were stratified in two groups with normal (n=127) or low (n=88) CSF Aβ42 levels (cut-off 450 ng/L). Cognitive scores from the Mini Mental State Examination (MMSE) and the Neurobehavioral Cognitive Status Examination (Cognistat) were used as continuous dependent variables in linear regression. WML load was used as a continuous independent variable and was scored with a visual rating scale. The regression model was corrected for possible confounding factors.

Results – WML were significantly associated with MMSE and all Cognistat sub-scores except language (repetition and naming) and attention in patients with normal CSF Aβ42 levels. No significant associations were observed in patients with low CSF Aβ42.

Conclusions – WML were associated with affection of multiple cognitive domains, including delayed recall and executive functions, in patients with normal CSF Aβ42 levels. The lack of such associations for patients with low CSF Aβ42 (i.e. with evidence for amyloid deposition), suggests that amyloid pathology may obscure cognitive effects of WML.

Paper III

White matter lesion subtypes and cognitive deficits in patients with memory impairment

Aim: To analyze the relationship between periventricular (PV) and subcortical (SC) white matter lesions (WML) and cognitive function in patients with memory impairment.

Methods: 253 patients with Global Deterioration Scale score ≥3 referred to a university based memory unit due to memory complaints were included (mean age 69.7 years, 124 females). Cognitive function was assessed with Mini Mental State Examination (MMSE) and Neurobehavioral Cognitive Status Examination (Cognistat) and full test results were available for 217 patients. PV and SC WML loads (semi-quantitative rating on axial T2-MRI scans) were used in linear regression as predictors of cognition.

Results: MMSE was significantly correlated with SC WML ($p=0.005$), but not with PV WML ($p=0.19$). Cognistat tests for orientation, comprehension, visuoconstruction, calculation, similarities, and judgment were negatively correlated with SC WML ($p<0.01$), and verbal memory with parieto-occipital SC WML ($p<0.05$). Visuoconstruction and calculation were negatively correlated with PV WML ($p<0.05$). Parieto-occipital WML were more strongly related to cognition than fronto-temporal WML. Only SC WML were significantly correlated with cognition when PV and SC WML were entered simultaneously in the regression model.

Conclusions: The results suggest that mainly SC WML are related to cognitive loss, and that WML in parieto-occipital regions have stronger negative effects on cognition than WML in fronto-temporal regions. The findings further suggest a possible sequential development of WML (PV WML → SC WML).

Paper IV

White matter lesion load increases the risk of low CSF Aβ42 in apolipoprotein E ε4 carriers.

Background: White matter lesions (WML) are age-related manifestations of ischemic cerebrovascular disease, which increase the risk for Alzheimer's disease (AD). The apolipoprotein E ε4 (ApoE-ε4) genotype is an established risk factor for late onset AD and has been related to low levels of Aβ42 in the cerebrospinal fluid (CSF) and to cerebrovascular disease. The aim of the present study was to analyze the relationship between WML, ApoE-ε4 genotype, and low CSF Aβ42 in patients recruited from a memory unit.

Methods: 235 patients from 40 to 91 years of age (mean 69 years; 119 women) with different degrees of cognitive impairment were included from a university based memory clinic. Brain MRIs were performed and periventricular (PV) and subcortical (SC) WML were rated on axial T2 MRI images. ApoE genotype and CSF Aβ42 levels were analyzed. Patients were stratified in three groups according to WML load. Group 1 (n=70) had no WML or only small amounts of PV or SC WML, WML group 2 (n=83) had high amounts of PV WML and low amounts of SC WML, and WML group 3 (n=82) had high amounts of both PV and SC WML. In the three WML groups, ApoE-ε4 genotype was used in logistic regression as predictor for low CSF Aβ42 (cut-off value ≤450 ng/L). Age and hypercholesterolemia were entered as co-variates in the regression model.

Results: The odds ratio (OR) of having low CSF Aβ42 was significantly increased in the presence of ApoE-ε4 only in WML group 3. WML group 1 (OR [95%CI] 1.39 [0.49, 3.98], p=0.53); WML group 2 (OR [95%CI] 2.38 [0.86, 6.56], p=0.093); WML group 3 (OR [95%CI] 3.69 [1.38, 9.88], p=0.009).

Conclusion: A high WML load may interact with the ApoE-ε4 genotype and increase the risk for reduced CSF Aβ42 in patients with cognitive impairment.

Paper V

Cingulum fiber diffusivity and CSF T-tau in patients with subjective and mild cognitive impairment

Background: Diffusion Tensor Imaging (DTI) and CSF biomarkers are useful diagnostic tools to differentiate patients with mild cognitive impairment (MCI) from normal controls, and may help predict conversion to dementia. Total Tau protein (T-tau) and DTI parameters are both markers for axonal damage, thus it is of interest to determine whether DTI parameters are associated with elevated CSF T-tau levels in patients with cognitive impairment.

Methods: Patients with subjective cognitive impairment (SCI) and MCI were recruited from a university based memory clinic. Regions of interest were used to determine fractional anisotropy (FA), radial (DR) and axial (DA) diffusivity in known white matter tracts in patients with MCI (n=39) and SCI (n=8) and 26 cognitively healthy controls.

Results: Significant lower FA and higher DR values were observed in patients with pathological vs. patients with normal CSF T-tau levels and vs. controls in left posterior cingulum fibers. T-tau values were negatively correlated with FA and positively correlated with DR values in the posterior cingulum fibers.

Conclusion: Cingulum fiber diffusivity was related to T-tau pathology in SCI/MCI patients and altered DR may suggest that loss of myelin contributes to early white matter changes in patients at risk of developing Alzheimer´s disease.

4. GENERAL DISCUSSION

Is there a link between white matter lesions and amyloid pathology?

Previous studies point to a link between ischemic damage in white matter and cortical Alzheimer pathology, but no causal relationship has been definitely established. Overlapping risk factors between cerebrovascular disease (CVD) and Alzheimer´s disease (AD) suggest a link between the two disease processes. It has been argued that non-genetic late-onset AD is triggered by CVD, and therefore should be regarded as a primary vascular disease (de la Torre, 2002). This hypothesis is supported by neuropathological and experimental studies which show that hypoxia influences amyloid percursor protein (APP) metabolism and increases deposition of amyloid-β (Aβ) (Jendroska et al., 1995; Sadowski et al., 2004). In addition, hypoxia has been shown to increase the β-secretase cleavage of APP leading to an increased production of Aβ42 protein in mice (Sun et al., 2006).

A number of studies have shown that the amount of amyloid plaques increases with age, and autopsies of elderly without cognitive impairment have revealed patho-histological findings similar to those seen in AD (Green et al., 2000; Knopman et al., 2003). Age, which is also strongly related to WML, therefore represents an important confounding factor when investigating the relationship between WML and amyloid pathology. A recent study even suggests a relationship between age and CSF Aβ42 in cognitively healthy individuals (Bouwman et al., 2008). However, cerebrovascular changes, like WML, were not corrected for in these studies. The main finding of paper I was that WML increased the risk of having pathological levels of CSF Aβ42. This relationship was observed despite that there was no significant difference in age between patients with normal and pathological CSF Aβ42 levels (see table 1 later in text). The findings in paper I therefore further support previous evidence for links between age, hypertension, hyperhomocysteinemia and WML, as well as between hypercholesterolemia and ApoE-ε4 and low CSF Aβ42. Hypercholesterolemia is not only a vascular risk factor but has previously also been directly implicated in amyloid formation as a result of altered metabolization of APP (Wolozin, 2004; Ehehalt et al., 2003; Rebeck, 2004). In accordance with previous studies, we did not find that hypercholesterolemia was related to WML in the age group studied in paper I (Breteler et al., 1994; Sawada et al., 2000). WML and hypercholesterolemia could therefore independently contribute to low CSF Aβ42 in subgroups of patients

(Casserly and Topol, 2005). However, our findings support the association between WML and the two cerebrovascular risk factors, hyperhomocysteinemia and hypertension (Vermeer et al., 2002).

As shown in the introduction (figure 1), MRI scans of patients without known memory problems also indicate an enhanced accumulation of WML in the age group studied in paper I (Masana et al., 2003). WML therefore probably affect the majority of the elderly population, and non-ischemic cases are expected to be rare in older patients. As age-associated WML prevalence obviously occurs prior to that of increased AD prevalence (cf. Figure 1), the results of paper I suggest that WML could predispose susceptible patients for development of AD. Our findings clearly support the hypothesis that white matter lesions are linked to amyloid pathology as measured by CSF Aβ42.

Do ApoE genotype and white matter lesions interact in the development of amyloid pathology?

As both ischemia and ApoE-ε4 have been related to ß-amyloid metabolism, we hypothesized that there may be a connection and possible interaction between ischemic WML, ApoE-ε4 and degenerative processes that involve APP metabolism. The negative correlation between age and CSF Aβ42 may be induced by ApoE-ε4 status (Peskind et al., 2006). However, due to the very strong connection between increasing WML and increasing age (Masana et al., 2003), if not considered, both age and WML may confound the analysis of ApoE-ε4/CSF Aβ42 relationships. Experimentally, ischemia has been proven to elicit increased APP expression (Nihashi et al., 2001). Accordingly, increased amounts of APP have been described intra-axonally in cases with subcortical ischemia (Akiguchi et al., 1997). Evidence has been presented for effects of ApoE-ε4 on processing of APP, as well as effects on binding, aggregation and deposition of amyloid (Strittmatter et al., 1993; Sanan et al., 1994; Selkoe, 2003). Interaction between ischemia and ApoE-ε4 in the development of amyloid pathology may be studied in humans by comparing the effect of ApoE-ε4 on CSF Aβ42 in patients with different grades of WML severity, as shown on MRI scans. In paper I we described an association between the total amount of WML and low CSF Aβ42. In a possible interaction between cerebrovascular disease and AD, severe subcortical WML may have a more pronounced effect than periventricular

lesions that are more distant from the cortex. In addition, the ApoE-ε4 genotype may influence the metabolism of APP (Strittmatter et al., 1993) facilitating a drop in CSF Aβ42. In paper IV, patients with available analysis of CSF and ApoE genotype from paper III were stratified according to WML load. As described in paper III, high amounts of subcortical WML were only seen in patients with periventricular WML. In contrast, high amounts of periventricular WML were seen in patients without subcortical affection. The distribution of PV and SC WML may therefore suggest a sequential development of WML, providing the biological basis for partitioning cases in groups with less and more WML.

The results in paper IV suggest that there may be an interaction between WML and ApoE-ε4 in the development of low CSF Aβ42. The relationship between WML and Aβ42 was dependent on the presence of ApoE-ε4 and the results demonstrate that the combination of ApoE-ε4 and high WML load may increase the odds of having low CSF Aβ42. After regressing out age and hypercholesterolemia in the group analysis, we found that the odds of having a low CSF Aβ42 value was significantly increased in the presence of ApoE-ε4 only in patients with high WML load (WML group 3). The findings in paper IV therefore support the hypothesis that the co-existence of high white matter lesion load and the ApoE-ε4 allele increases the risk of having low CSF Aβ42.

Are white matter lesions related to cognitive loss, and does the location of white matter lesions matter?

Several studies have reported associations between WML and cognitive impairment (e.g. Gold et al., 2007; Au et al., 2006; Longstreth et al., 1996). The strongest associations between WML and cognition involve cognitive functions that are mainly dependent on temporal and frontal structures, including associative pathways (Jokinen et al., 2006).

Paper II describes WML-dependent cognitive loss in a population without evidence of amyloid deposition based on CSF-analysis. While the results showed a consistent correlation between increasing WML and cognitive loss, larger effect sizes (higher B-values) and higher levels of significance suggested a stronger relationship in the group with normal Aβ42 levels than in the one with low values. This may be

because the more subtle effects of WML may be obscured by the more predominant effects on cognition of cortical amyloid deposition in patients with low CSF Aβ42. The results delineate a profile of cognitive loss resulting from WML alone. As the effect sizes were largest on categories of verbal memory, similarities, judgment and visuoconstruction, the results presented in paper II support earlier reports suggesting that WML are related to cognitive domains that are mainly dependent on temporal and frontal structures, as well as associative pathways.
The association between increased WML and reduced verbal memory (after exclusion of cases with CSF-evidence for amyloid deposition) suggests that reduced delayed memory is also part of the spectrum of vascular cognitive disorder.

The results of paper III further indicate that subcortical (SC) WML are more strongly related to cognitive function than periventricular (PV) WML. These findings are supported by some studies (Baum et al., 1996; Delano-Wood et al., 2008), whereas others have reported that PV WML are more strongly related to cognition (de Groot et al., 2000; Burns et al., 2005). Despite these inconsistencies, it may be reasonable to conclude that both PV and SC WML may have effects on cognition. It has been argued that since PV WML probably affect long distance association fibers, they are more prone to affect cognitive function (de Groot et al., 2000). PV and SC WML often co-exist and SC WML are likely to affect cortical-subcortical networks.

In paper III all patients with high SC WML loads also had high loads of PV WML. This suggests that SC WML may represent a more advanced white matter affection than PV WML, thereby explaining why we found that they were more strongly related to cognitive impairment. We further examined whether WML in fronto-temporal (F-T) and parieto-occipital (P-O) regions affect cognition differently. We found that WML in P-O regions were more strongly related to cognitive impairment than WML of the F-T regions. In paper II we observed a relationship between total WML (Wahlund scale) and verbal memory in the entire patient group. In paper III we did not observe a significant relationship between whole brain PV and SC WML scores and verbal memory. The discrepancy with regard to WML and memory may be due to the different scales used in the two papers, and also to the effect of AD pathology on cognition (see below). However, P-O SC WML were significantly related to reduced verbal memory. White matter in the parieto-occipital regions contains fiber networks that are important for memory function. Disruption of cortical regions in these areas (e.g. posterior cingulate and lateral parietal cortex) may

thus contribute to impaired memory (Buckner et al., 2005). This could be a plausible explanation for our findings that only WML of the P-O regions were negatively correlated with memory. Previous studies, which have reported a lack of relationship between WML and memory, have not analyzed possible differences between F-T and P-O WML (Baum et al., 1996; Delano-Wood et al., 2008). Even though P-O WML showed an overall stronger relationship with cognition, the results in paper III also indicated that SC WML of the F-T regions were strongly and negatively correlated with several cognitive domains including visuoconstruction, similarities and judgment. This is in line with other studies, which have related WML to deficient frontal-subcortical network functions (executive functions and processing speed) (Delano-Wood et al., 2008; Inzitari et al., 2000).

Paper III also focused on describing the subtypes of WML and their relationship to cognitive function. The question whether PV and SC WML represent different disease mechanisms or whether they represent a continuum of cerebrovascular disease, remains unresolved. However, it has been observed that WML often extend from periventricular areas into subcortical white matter with increasing WML volume and severity (DeCarli et al., 2005). We found that PV WML were present in a younger age group than SC WML. This could be explained by the theory presented by DeCarli and colleagues suggesting that PV WML occur before more advanced SC WML.

The etiopathology of PV and SC WML are similar and ischemic events play an important part (Ward and Brown, 2002). PV and SC regions are perfused by pial end arterioles (De Reuck, 1971), with PV regions lying in the distal part of the perfused region. Arteriolosclerosis starting distally in deep penetrating end arterioles could explain that PV WML may occur before SC WML. As previously shown, we also found that PV and SC WML were strongly correlated. The strong correlation between the PV and SC WML subtypes described here suggests etiopathological similarities, but as mentioned, differences in tissue response and vascular risk factors between WML in the two regions have been described (Simpson et al., 2007; Lazarus et al., 2005). The hypothetical sequential nature of PV and SC lesions and putative etiopathological differences between the lesion subtypes need to be clarified in prospective studies. If PV lesions herald white matter disease, this early stage may be important for the initiation of therapy for patients at risk for more severe affection.

Collectively, the findings of this thesis support the hypothesis that WML are related to reduced cognitive function. The findings further suggest that the localization of WML matters, but this may be because SC WML represent a more advanced stadium than WML in PV regions.

Are diffusion tensor imaging parameters related to Tau pathology and may these changes be part of the development of cognitive impairment?

Over the last two decades Diffusion Tensor Imaging (DTI) has emerged as an important non-invasive technique to investigate disease processes related to white matter changes and axonal damage. As discussed earlier, there seems to be a link between cerebrovascular disease and AD, and both cerebrovascular changes and AD pathology probably occur years before the manifestation of cognitive impairment and dementia. To detect early events in the development of cognitive impairment, the combination of advanced neuroimaging like DTI and the use of biomarkers (e.g. from CSF) must be applied before full-blown dementia occurs. Patients with subjective and mild cognitive impairment (SCI and MCI) are at risk of developing dementia (Reisberger and Gauthier, 2008). These patients therefore are of high interest when studying disease development. Several DTI studies have revealed reduced white matter integrity in MCI and AD patients. In addition, decreased connectivity from areas related to the memory network (hippocampus and posterior cingulate cortex) to the rest of the brain has been described (Fellgiebel et al., 2005; Zhang et al., 2007; Zhou et al., 2008).

As both DTI and CSF T-tau alterations have been related to axonal damage, paper V aimed to examine the relationship between these two parameters in patients at risk of developing AD. The patient population included both SCI and MCI, and T-tau was used to stratify the group. In Paper V we found that elevated CSF T-tau values were related to lower FA and increased DR in SCI/MCI patients. Signs of decreased FA and increased DR in posterior cingulum fiber tracts of these patients indicate early tau-related white matter alterations. Increased DR may reflect loss of myelin (Pierpaoli et al., 2001; Song et al., 2003; Song et al., 2002), but DR is a sensitive measure, possibly also reflecting distant pathological processes (Budde et al., 2007). Our findings in the left posterior cingulum bundle are in line with previous studies of MCI patients (Fellgiebel et al., 2005; Zhang et al., 2007). The significant FA and DR alterations we observed in the genu of corpus callosum may indicate that

early white matter pathology also appear in neocortical connections in patients at risk of developing AD. Paper V did not reveal group differences in DA, but axon loss with transient effects on DA can not be excluded (Concha et al., 2006; Sun et al., 2008). Moreover, the observed association between DR and CSF T-tau levels may reflect underlying axonal affection (Teunissen et al., 2005).

In addition to axonal damage, Tau pathology has also been related to hippocampal atrophy (Adalbert et al., 2007; de Leon et al., 2007). In a subsample of the cohort studied in paper V, we have reported associations between pathological CSF biomarkers and reduced hippocampal volume and cortical thinning (Fjell et al., 2008). We found no association between hippocampal volume and directional diffusivity in the sample studied in paper V, but we did observe that both FA/DR in white matter tracts and hippocampal volume were associated with CSF T-tau levels. This fully agrees with the findings of Salat et al. (2008) suggesting that white matter alterations (demyelination or reduced axonal integrity) may represent an additional mechanism, besides cortical degeneration, in the AD process.

The results of paper V support the hypothesis that Tau pathology in the CSF may be related to axonal damage as measured with DTI. Since Tau pathology in patients with cognitive impairment is related to AD, the observed DTI changes may represent early events in the disease process. Paper V further substantiates the importance of using CSF analysis and neuroimaging to differentiate patients with cognitive impairment at an early stage. However, follow up studies are needed to detect potential differences in disease development between these subgroups of SCI/MCI patients.

Methodical aspects and limitations

The patients in this thesis were all admitted to a university based memory clinic due to cognitive impairment of different degrees. As all patients sought help because of cognitive problems, one may expect these patients to have more pathologic findings (e.g. WML) than would be observed in the average population without overt cognitive problems. Due to possible paradoxical relationships between cerebrovascular risk factors (e.g. blood pressure levels) and WML when studied in high age groups (Turner and Fornage, 2002), paper I included patients between 40-75 years of age. In paper II-IV, inclusion was less restrictive than in paper I and no age limit was used in

the inclusion criteria. The patient cohort studied in the subsequent papers II-IV was therefore larger than in paper I. The age range extended from 40 to 91 years.

Path analysis, which is a form of multiple regression analysis (Bollen, 1989) was used to test the hypothesis in paper I. The path analysis model implies a set of covariances among all pairs of variables. Adding, removing or changing the direction of an effect arrow means changing the set of regression equations. Path analysis tests whether or not postulated effects, based on the theory presented, correspond to the observed covariance structure of the data. Path analysis does not prove causality, but it tests whether the data set allows or denies the postulated effects. The path analysis model which had the best fit in paper I did not include a direct effect arrow from age to CSF Aβ42 levels. However, the design of the path analysis model corrects for a possible relationship between these two factors, and still suggests that WML load may be associated low CSF Aβ42 levels. Table 1 shows that there were no significant differences in age between patients with low and normal CSF Aβ42 levels, but a significant difference in WML load which was confirmed by testing with Students t-test.

Table 1: Age and WML load of patients with pathological and normal CSF Aβ42 levels in paper I

	Aβ42 ≤ 450 n = 58	Aβ42 > 450 n = 63	Mean difference (95% CI of the difference)	p-value
Age	66.6 (6.9)	65.4 (7.5)	-1.2 (-3.7;1.4)	0.37
WML load	5.5 (3.3)	4.1 (2.9)	-1.3 (-2.4;-0.2)	0.02

Numbers are mean (SD) unless otherwise given. Student's t-test.

When interpreting the results from studies investigating the relationship between WML and cognition, two important issues have to be taken under consideration:

1) What population was studied? Effects of WML on cognition in patients with cognitive impairment, as in paper II and III, may differ from effects of WML observed in a cohort of normal elderly. Also, as shown in paper II, in selected AD patients, the pronounced effects of amyloid deposition and neurofibrillar pathology

may make the effects of WML more subtle and less easy to discern in cognitive tests. The effect of WML on cognition in the elderly has recently been reviewed (Frisoni et al., 2007). When compared to the effects of a neurodegenerative disorder such as AD, the effects are relatively small. This may explain why the effects of WML on cognition are difficult to detect in the presence of AD.

2) What scale or method was used to quantify PV and SC WML? There are various methods to quantify PV and SC WML. In our study we defined PV WML as WML adjacent to the ventricles. If these lesions extended more than 1 cm away from the ventricle and further into deep white matter, the part of the WML, which was more than 1 cm away from the ventricle wall, was rated as SC WML. Other studies (e.g. van Straaten et al., 2008), define all WML adjacent to the ventricle wall as PV WML. This means that the WML defined as "high levels of PV WML" in the some studies would have been defined as high levels of PV and high levels of SC WML in others, even though they describe the same phenomenon: advanced WML extending from the periventricular regions into deep subcortical areas.

For assessment of cognitive function in paper II and III, the Neurobehavioral Cognitive Status Examination (Cognistat) (Kiernan et al., 1987; Schwamm et al., 1987) was used. The Cognistat is primarily a screening test, which has gained considerable popularity. Like in all test situations, anxiety and stress may cause the patient to perform worse than he/she normally would. Using experienced staff trained for the specific purpose can minimize this problem. In the memory unit at Akershus University Hospital, where the testing was conducted, the staff has many years of clinical experience, and the Cognistat test has been in use in the unit for almost a decade.

Papers I-V were all cross-sectional studies with relative small patient samples. Cross-sectional data can be used to assess the prevalence (total number of cases in a population at a given time) of acute or chronic conditions. However, cross-sectional studies are descriptive studies where cause (exposure, e.g. age, hypertension) and consequence (disease, e.g. WML, CSF Aβ42) are measured simultaneously in a given population. A cross-sectional study therefore provides a "snapshot" of the characteristics of a measured disease or condition in a population at a given point in time. Cross-sectional studies are very useful to explore relationships between exposure and measured disease/condition. However, since exposure and disease status are measured at the same point in time, such studies can not clarify whether the

exposure preceded or followed the disease, and therefore the relationship between exposure and disease can not be definitely established. Prospective, longitudinal studies observe the course of disease development as several measurements are performed over a period of time. Exposure to certain possible risk factors may be followed before a certain disease or condition develops. In papers I-IV the data were collected retrospectively. This obviously resulted in some missing data, making the samples smaller.

When studying acquired risk factors, as was done in paper I, a large patient cohort is needed. In paper I, only 121 patients were available for studying the relationship between acquired risk factors for cerebrovascular disease, WML and CSF Aβ42. The findings therefore need to be confirmed in larger patient sample and, preferably, in a longitudinal study. However, as discussed earlier, many studies have shown that cerebrovascular disease and beta amyloid processing are somehow connected. Despite the small patient sample, paper 1 demonstrates a link between these two important factors in the development of AD.

In paper V, the use of two different scanners with slight differences in acquisition matrices may possibly have introduced biases, but the reported effects were observed in both samples and scanner site was regressed out in all analyses so it is not likely that this introduced a systematic bias in the results. Another weakness of paper V was that controls were not tested formally with regard to cognitive performance. To ensure that controls are "cognitively healthy", it is important to include formal testing of the control cohorts in future studies.

According to criteria for MCI, in addition to subjective memory impairment, preserved general intellectual function, and no or very mild ADL problems, objectively verifiable memory impairment or deficits in other cognitive domains must be present (Petersen et al., 1999, Winblad et al., 2004). Patients with early cognitive deficits may fall into either GDS group 2 and 3, e.g. based on pre-morbid cognitive capacity and the fact that cutoffs for cognitive tests are group-based and not individualized. It has been suggested that AD may be identified earlier if intra-individual changes are considered rather than cutoffs based on group norms (Storandt et al., 2006). In order not to exclude patients with very early disease, patients with subjective memory complaints and clinical dementia rating (CDR) = 0.5 but with screening test results above cut-off, corresponding to criteria for SCI (or GDS 2) and to "CDR 0.5/uncertain dementia" (Morris et al., 2001), were also included in paper V.

Analysis of the entire SCI/MCI group and for the MCI group alone were performed, giving much the same results, but with lower levels of significance when excluding SCI patients from the analysis. The latter effect is likely to reflect the smaller sample size. The SCI group alone was not large enough for separate analysis.

Comments

The exact cause of white matter lesions associated with age and cognitive decline have not yet been established. As discussed, the main hypothesis is that chronic hypoperfusion of the brain and/or disruption of the blood-brain barrier are the main contributors to these changes. This is supported by molecular studies showing higher contents of hypoxia-associated proteins in WML than in normal white matter (Fernando et al., 2006). Other changes associated with WML include apoptosis of oligodendrocytes, increased microglial activation, and myelin attenuation (for discussion see Simpson et al., 2007). Oligodendrocytes comprise the largest component of white matter, their main function being the insulation of the axons. Recent studies suggest that myelinating processes of oligodendrocytes contain N-Methyl-D-aspartate (NMDA) receptors, which render them sensitive to damage when extra cellular glutamate is released during ischemia (Káradóttir et al., 2005). More research related to molecular events during ischemia is needed, but these or similar mechanisms could help explain how hypoperfusion of the cerebral white matter could contribute to dysmyelination and white matter degeneration. The findings in paper V show how the combination of CSF analysis and DTI is essential to detect early white matter changes in subgroups of patients before they are visible on conventional MRI. It remains to be investigated whether these early alterations are related to cerebrovascular risk factors.

Recent research suggests many similar risk factors for degenerative and vascular cerebral disease such that there is little doubt that these disease processes are somehow related. Findings presented in this thesis likewise suggest a link between vascular and degenerative disease processes. However, it is not yet clear how events in gray and white matter are related. White matter changes seem to play an important role in the development not only of vascular, but also of degenerative cognitive impairment and dementia. As previously discussed, white matter changes have been

observed before cortical degeneration occurs, and cerebrovascular changes are common in AD.

AD is considered to be a multifactorial disease where both genetic factors and cerebrovascular changes play important roles. It is easily conceivable that various pathological processes in different degrees may lead to a common final pathway.

5. CONCLUSIONS AND FURTHER PERSPECTIVES

Both cerebrovascular changes and ApoE genotype are related to amyloid pathology in CSF

The findings presented in this thesis supports the hypothesis that there is a link between cerebrovascular disease and amyloid pathology. The age-independent relationship between WML and low CSF Aβ42 levels in paper I suggests that chronic ischemia may increase the risk of developing AD pathology. Paper IV further supports this hypothesis and suggests an interaction between ischemia and genetic predisposition in the development of AD pathology. Age, hypertension and hyperhomocysteinemia are further confirmed as important risk factors for ischemic WML. Since ApoE-ε4 carriers with high WML loads were found to exhibit low CSF Aβ42, these particular patient cohorts may benefit from early treatments of e.g. hypertension and hyperhomocysteinemia in order to prevent further disease development.

White matter lesions are related to cognitive function

This thesis also confirms that WML are associated with impairments of multiple cognitive domains, including delayed recall and executive functions. By demonstrating this relationship in a patient group without CSF findings of amyloid pathology, the hypothesis that WML alone may affect cognitive function receives considerable support. Our findings suggest that in the group with low CSF Aβ42 the more subtle effects of WML may be obscured by the more predominant effects that cortical amyloid pathology may have on cognition.

Subcortical WML are more strongly related to cognition than periventricular WML

An important finding of our studies was that SC WML were more strongly related to reduced cognitive function than PV WML. PV WML were observed in a younger age group than SC WML, and all patients with high loads of SC WML also had high loads of PV WML. This suggests that SC WML may represent a more advanced stage of microvascular disease than PV WML. The stronger relationship between SC WML and cognition supports the latter interpretation.

DTI and CSF analysis are essential to differentiate early disease mechanisms

As presented in paper V, DTI combined with CSF biomarkers could be shown to be useful tools to identify early disease related changes in patients at risk of developing AD. In these patients early pathogenetic events may be related to axonal damage in fiber tracks affecting the memory network. These observations bear on the important issue of early identification of disease processes, which need to be understood for the development of disease modifying drugs.

In summary, the results presented in this thesis add substantial new information concerning white matter changes in the human brain. Even though our findings in human subjects are by necessity descriptive and correlative, we have every reason to assume that white matter changes may contribute to the development of cognitive impairment and AD pathology. As all results presented in this thesis are based on cross-sectional data, our findings need to be confirmed in prospective and experimental studies.

Some objectives of further studies might include the following approaches:

I. to longitudinally study WML progression and compare this to the development of low CSF Aβ42
II. to study WML progression and its relationship to cognitive decline and cortical atrophy
III. to study cerebrovascular changes in gene modified hypertensive rats and relate this to amyloid deposition, and if possible also to ApoE-ε4 status
IV. to longitudinally study DTI changes in SCI/MCI patients and compare this to CSF biomarkers and cognitive decline
V. to study how early DTI changes are related to vascular risk factors
VI. to study molecular events related to ischemia and hypoperfusion

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